



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA-2018-C-0617]

Listing of Color Additives Exempt from Certification; Silver Nitrate

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the color additive regulations to provide for the safe use of silver nitrate as a color additive in professional-use only cosmetics to color eyebrows and eyelashes. This action is in response to a color additive petition (CAP) filed by GW Cosmetics GmbH.

DATES: This rule is effective November 8, 2021. See section VIII for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing on the final rule by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. Electronic objections must be submitted on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on <https://www.regulations.gov>.
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper objections submitted to the Dockets Management Staff, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-C-0617 for "Listing of Color Additives Exempt from Certification; Silver Nitrate." Received objections, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

<https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Rachel Morissette, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740-3835, 240-402-1212.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the *Federal Register* of March 7, 2018 (83 FR 9715), we announced that we filed a color additive petition (CAP 8C0312) submitted by GW Cosmetics GmbH (GW), c/o EAS Consulting Group, LLC, 1700 Diagonal Rd., Suite 750, Alexandria, VA 22314. The petition and its supporting documents proposed to amend the color additive regulations in part 73 (21 CFR part 73), *Listing of Color Additives Exempt from Certification*, to provide for the safe use of silver nitrate as a color additive, at a level of up to 4 percent by weight in the final product, in professional-use only cosmetics to color eyebrows and eyelashes in persons age 16 and older.

Silver nitrate is a highly purified inorganic compound obtained as the recrystallized precipitate from the concentrated reaction mixture of silver and excess nitric acid at elevated temperatures, followed by drying the decanted, filtered, and washed crystals. Silver nitrate has the chemical formula AgNO_3 . Although silver nitrate is colorless, when it comes into contact with argentaffin, the melanin-rich protein filaments in the hair, it is reduced to black-brown metallic silver, which remains in the filaments (Ref. 1). GW formulates the silver nitrate into a viscous gel, which limits migration of the gel components into the eye during and after the application procedure, thereby minimizing potential extraneous staining or irritation.

II. Safety Evaluation

Under section 721(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379e(b)(4)), a color additive cannot be listed for a proposed use unless the data and information available to FDA establish that the color additive is safe for that use. Our color additive regulations in § 70.3(i) (21 CFR 70.3(i)) define “safe” to mean that there is convincing evidence establishing with reasonable certainty that no harm will result from the intended use of the color additive. As part of our safety evaluation to establish with reasonable certainty that a color additive is not harmful under its intended conditions of use, we consider the color additive’s

manufacturing and stability; the projected human exposure to the color additive and any impurities resulting from the petitioned use of the color additive; the additive's toxicological data; and other relevant information (such as published literature) available to us.

A. Estimated Dermal Exposure

To support the safety of the intended use of silver nitrate, GW provided estimates of the systemic exposure to silver from the petitioned use of silver nitrate using various published dermal absorption values. However, as we explain in a separate memorandum (Ref. 2), we consider the most comprehensive measure of skin penetration of silver to come from a recent published mass balance percutaneous penetration study that determined the distribution of silver penetrating the different layers of human skin (Ref. 3). Therefore, we used these published dermal absorption values, expressed as a dermal absorption percentage of the amount of silver applied, and assumptions made in GW's exposure estimate, to estimate that the dermal exposure to silver from the intended use of silver nitrate would be 0.15 micrograms (μg) silver/person (p)/day (d) per application. Since the exposure to silver could also be affected by the duration of the silver nitrate's contact with the skin at the application site, we further refined the exposure based on an exaggerated upper-bound application time of 3 minutes (Ref. 2). Thus, the maximum estimated dermal exposure to silver from the intended use of silver nitrate to color eyebrows and eyelashes is estimated to be 0.3 nanograms (ng)/p/d per application and exposure to silver nitrate is estimated to be 0.5 ng/p/d per application (Ref. 2).

B. Acceptable Intake Level for Silver

In the evaluation of the safe use of an ingredient or substance that can be absorbed systemically (e.g., a color additive for use in a cosmetic), we consider overall probable exposure (Ref. 4). We calculated the oral cumulative estimated daily intake (CEDI) of silver to be 72 $\mu\text{g}/\text{p}/\text{d}$ in our previous evaluations (Ref. 5). The conservative estimate of systemic exposure to silver from its color additive use in a high-viscosity gel formulation applied to eyebrows and eyelashes (0.3 ng/p/d per application) is approximately 0.0004 percent of the CEDI (Ref. 4).

However, the systemic exposure to silver is likely to be far less than the estimate of 0.3 ng/p/d per application due to three default factors and assumptions used in that estimate. First, a dermal retention factor of 0.1 (10 percent) for a “leave-on” (i.e., not intended to be rinsed off) product was used, although excess gel is intended to be removed as directed; second, a 20 percent skin “reach” factor (i.e., 20 percent of the applied silver nitrate gel is in contact with the skin) was used, though this number is likely much less, provided the gel is thoroughly removed from the eyebrows or eyelashes as directed; and third, a 1 in 10 day use factor was used, which is likely to be conservative when considering exposure over a lifetime. For example, GW notes that the coloring effects should last up to 6 weeks. Therefore, if an individual decreases their use from once every 10 days to once every 2 weeks, there would be a 30 percent decrease in the exposure to silver. Furthermore, silver binds tightly to protein and would not be expected to transfer from the protein in the hair follicles (Ref. 4).

Considering the very low percentage (0.0004 percent) of the CEDI represented by our estimated systemic exposure from the intended use of silver nitrate as a color additive for dyeing eyebrows and eyelashes, and the likelihood that probable systemic exposure to silver is orders of magnitude lower than the 0.3 ng/p/d per application estimate, we conclude that the exposure to silver from the petitioned intended use is negligible, and it does not impact the CEDI of silver (Ref. 4).

C. Toxicological Considerations

To establish that silver nitrate is safe for use as a color additive to color eyebrows and eyelashes, GW provided data from two in vitro ocular irritation assays conducted with the proposed silver nitrate gel. Both of these in vitro studies, using colorimetric measurements as predictors of ocular irritancy, indicate that the silver nitrate gel product contains severe eye irritating ingredient(s). However, the color of this product interferes with colorimetric measurement portion of these studies, limiting the utility of these studies to non-colorimetric dependent portions of the assessment. Colorimetric results cannot be used to determine the

ocular irritancy of a colorant such as silver nitrate; therefore, the assays provided only limited value to the current safety assessment. Nevertheless, the color of silver nitrate does not affect the histological assessment portion included in one of the in vitro studies. The histopathological results from one in vitro assay performed on bovine corneas treated with the silver nitrate gel did not reveal any significant physical effects or potential for damage, even following a 10-minute continuous exposure with full immersion (Refs. 5 and 6). In comparison, GW's proposed upper-bound application time of the silver nitrate gel is only 3 minutes. Additionally, the viscosity of the silver nitrate gel formulation limits entry into the eye during and after application to eyelashes. The ocular exposure to silver nitrate would be incidental and would initiate ocular tearing, which would dilute the silver nitrate concentration (Ref. 6). Additionally, we are requiring the instruction "Rinse eyes immediately if product comes into contact with them" on the label of cosmetic products containing this color additive. We expect this instruction will further minimize the chances of potential harm. Therefore, we expect no permanent ocular damage (Ref. 6).

GW also submitted results from a single-application, intended-use study in human subjects. The study included a pretreatment step with a preparation gel not containing silver nitrate to open hair cuticles prior to application of GW's silver nitrate gel to both eyebrows and eyelashes. During and after the study, only two adverse effects were identified in a limited number of users, which included burning sensations in the eyes (most occurrences were "slight" in degree and lasted less than 1 minute after the removal of the product, as self-reported by the study subjects) and skin staining primarily beneath the eyebrows (which was infrequent). We also found no clinically significant findings related to the eye (Ref. 7), which is consistent with the corneal histopathology findings. Based on these results, we conclude that potential ocular irritancy (i.e., burning sensations) and skin staining present minimal risks to safety.

Furthermore, we expect they will be mitigated by statements required to be on the label of a cosmetic product containing silver nitrate. See 21 CFR 73.2550(d)(2).

This final rule includes an age use limitation to help ensure that professionals apply silver nitrate cosmetics only to individuals with fully mature facial size and structural development. The human eye and associated structures generally reach full adult size and structural development by 12 years of age. Therefore, limiting the age use to 16 years and older provides a safety margin for those few individuals whose facial size and structures might not have fully developed by age 12 (Ref. 7).

This final rule includes a restriction on distribution or direct sale to consumers and a professional-use only limitation to increase the likelihood that professionals who are trained in and knowledgeable about applying cosmetics will apply the silver nitrate product. “Professional” in this rule means an individual who, as part of an occupation, is permitted by the jurisdiction in which the individual practices to apply cosmetics for dyeing eyebrows and eyelashes.

This final rule includes a limited application time to limit the amount of any potential systemic absorption of the silver nitrate. Silver nitrate absorption in the skin is time dependent; therefore, limiting the skin contact time will result in a negligible level of systemic absorption. We did not identify any evidence suggesting that GW’s intended conditions of use of silver nitrate are of toxicological concern (Ref. 6).

Based on the totality of the safety data and our conclusion that the systemic exposure to silver nitrate under the conditions of use is negligible, we conclude that there is a reasonable certainty of no harm from the intended use of silver nitrate in professional-use only cosmetics to color eyebrows and eyelashes of persons age 16 and older at a level of up to 4 percent by weight in the final product. To mitigate the risk of adverse effects from the use of silver nitrate in these cosmetic products, the labeling of the cosmetic product must include statements about the potential ocular irritancy and skin staining, an age use limitation, professional-use only designation, and limited application time.

III. Response to Comment

We received two comments in response to our filing of the color additive petition. One comment, however, did not address silver nitrate or color additives. The other comment claimed that the assumption that only trained beauticians or cosmetologists will be applying this product to consumers poses public health concerns because States have their own requirements regarding the licensure of makeup artists. The comment also stated that applying this product to the eyes and the surrounding area poses serious health concerns. The comment claimed that silver nitrate is considered highly toxic and that the gel containing the silver nitrate will travel down the hair shaft directly onto the skin and into the eye.

Regarding the professional-use only status of the product, we acknowledge that FDA does not regulate the professional practice of applying those cosmetics to consumers. This final rule includes a professional-use only limitation, along with a restriction on distribution or direct sale to consumers, to increase the likelihood that professionals who are trained in and knowledgeable about applying cosmetics will apply the silver nitrate product. As explained above, we reviewed data and information to establish that silver nitrate when applied as a gel under the conditions described herein is safe for its intended use. As demonstrated in the testing conditions that were described in the submitted petition, the silver nitrate gel product, when applied as intended, was not toxic and did not result in ocular damage. In this case, the intended use of silver nitrate is in specific professional-use only cosmetics, and we have determined that this intended use is safe.

Regarding the safety of applying this product to the eyes and the surrounding areas, we have determined, as explained in the discussion of our safety evaluation, that the intended use of silver nitrate as a color additive in certain cosmetic products is safe.

IV. Conclusion

FDA reviewed the data and information in the petition, and other available relevant material, and determined the petitioned use of silver nitrate, at a level of up to 4 percent by weight in the final viscous gel product, in professional-use only cosmetics to color eyebrows and

eyelashes is safe. We further conclude that the color additive will achieve its intended technical effect and is suitable for the petitioned use. Consequently, we are amending the color additive regulations in part 73 to provide for the safe use of this color additive as set forth in this document. In addition, based upon the factors listed in 21 CFR 71.20(b), we conclude that certification of silver nitrate is not necessary for the protection of public health.

V. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see FOR FURTHER INFORMATION CONTACT). As provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

VI. Analysis of Environmental Impact

We considered the environmental effects of this rule, as stated in the March 7, 2018, *Federal Register* notice of petition for CAP 8C0312. We have concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. We did not receive any new information or comments that would affect this determination. Our finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Staff (see ADDRESSES) between 9 a.m. and 4 p.m., Monday through Friday.

VII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Objections

This rule is effective as shown in the “DATES” section, except as to any provisions that may be stayed by the filing of proper objections. If you will be adversely affected by one or more provisions of this regulation, you may file with the Dockets Management Staff (see

ADDRESSES) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <https://www.regulations.gov>. We will publish notice of the objections that we have received or lack thereof in the *Federal Register*.

IX. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

*1. Memorandum from N. Hepp, Color Technology Branch, Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition (CFSAN), FDA to R. Morissette, Regulatory Review Branch (RRB), DFI, OFAS, CFSAN, FDA, September 10, 2021.

*2. Memorandum from H. Lee, Chemistry Review Branch (CRB), Division of Food Ingredients (DFI), Office of Food Additive Safety (OFAS), CFSAN, FDA to R. Morissette, RRB, DFI, OFAS, CFSAN, FDA, June 22, 2021.

3. Kraeling, M.E.K., V.D. Topping, Z.M. Keltner, et al. "In Vitro Percutaneous Penetration of Silver Nanoparticles in Pig and Human Skin." *Regulatory Toxicology and Pharmacology* (2018) 95: 314-322.

*4. Memorandum from M. DiNovi, OFAS, CFSAN, FDA to R. Morissette, RRB, DFI, OFAS, CFSAN, FDA, June 22, 2021.

*5. Memorandum from A. GonzalezBonet, CRB, Division of Food Contact Substances, OFAS, CFSAN, FDA to M. Swain, CRB, DFI, OFAS, CFSAN, FDA, April 7, 2017.

*6. Memorandum from M. Wyatt, Cosmetics Division, Office of Cosmetics and Colors, CFSAN, FDA to R. Morissette, RRB, DFI, OFAS, CFSAN, FDA, September 10, 2021.

*7. Memorandum from W. Chambers, Ophthalmology, Office of New Drugs, Center for Drug Evaluation and Research, FDA to R. Morissette, RRB, DFI, OFAS, CFSAN, FDA, September 2, 2021.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Foods, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 73 is amended as follows:

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Add § 73.2550 to read as follows:

§ 73.2550 Silver nitrate.

(a) *Identity.* The color additive silver nitrate is a purified inorganic compound obtained as the recrystallized precipitate from the concentrated reaction mixture of silver and excess nitric

acid at elevated temperatures, followed by drying the decanted, filtered, and washed crystals.

The color additive has the chemical formula AgNO_3 .

(b) *Specifications.* Silver nitrate shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by good manufacturing practice:

- (1) Arsenic, not more than 3 milligrams/kilogram (mg/kg) (3 parts per million (ppm)).
- (2) Cadmium, not more than 5 mg/kg (5 ppm).
- (3) Lead, not more than 10 mg/kg (10 ppm).
- (4) Mercury, not more than 1 mg/kg (1 ppm).
- (5) Volatile matter, calculated as water, not more than 0.1 percent.
- (6) Total color, not less than 99.9 percent.

(c) *Uses and restrictions.* The color additive silver nitrate may be safely used in externally applied professional-use only cosmetics intended to impart color to the eyebrows and eyelashes subject to the following restrictions:

- (1) The amount of silver nitrate in the cosmetic product shall not be more than 4 percent by weight.
- (2) The viscosity of the cosmetic formulation shall be not less than 120 Pascal-seconds (Pa·s) and not more than 180 Pa·s at normal temperature and pressure.
- (3) The cosmetic containing silver nitrate is not intended for use on persons under the age of 16.
- (4) Application of the cosmetic containing silver nitrate is not intended to exceed 1 minute and is intended to be followed by immediate removal.
- (5) The cosmetic containing silver nitrate is applied by a professional.
- (6) The cosmetic containing silver nitrate is not distributed or directly sold to consumers.

(d) *Labeling requirements.* (1) The label of the color additive and any mixture prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of

§ 70.25 of this chapter and include adequate directions to prepare a final product complying with the limitations prescribed in paragraph (c) of this section.

(2) The label of any cosmetic containing the color additive silver nitrate, in addition to other information required by law, shall contain the following statements: Contains silver nitrate. Silver nitrate may permanently stain skin with which it comes into contact. Silver nitrate may irritate the eyes. For application by professionals only for dyeing eyebrows and eyelashes, in accordance with the directions for use. Not for use on persons under the age of 16. Apply to eyebrows and eyelashes for no more than 1 minute, followed by immediate removal. Rinse eyes immediately if product comes into contact with them. Consult a physician if any irritation persists. Not for distribution or direct sale to consumers.

(e) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the Federal Food, Drug, and Cosmetic Act.

Dated: September 30, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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